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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ames et al.

Group Art Unit: 1614

Serial No. 10/038,135

Examiner: Jones, D.

Filed: October 20, 2001

Attorney Docket No. B00-001-2

For: *Primary N-hydroxylamines*

CERTIFICATE OF TRANSMISSION

I hereby certify that this comm is being transmitted by facsimile to the Comm for Patents 703-877-9306 on June 11, 2004.

Signature

Richard Aron Osman

OFFICIAL

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Examiner Jones:

Thank you for the Office Action dated Feb 26, 2004.

35USC103(a), Claims 62-131. Krishna et al. (1998, Journal of Medicinal Chemistry 41(18):3477-92) studied the effect of ring size, oxidation state and redox midpoint potentials of five or six-membered secondary nitroxides historically used as biophysical probes. The intermediate reduced forms of Krishna's nitroxides are the corresponding five or six-membered secondary hydroxylamines (e.g. compounds 1b, 2b, 5b, 6b, 9b, 11b-17b, 19b, 22b, 23b, 25b-27b, 29b, 36b-38b, 40b, 42b, 48b, 52b, 53b, and 55b; Krishna (1998) p.3478, col.2, lines 31-33).

Our claims require primary N-hydroxylamines, which are structurally and functionally different from the cyclic secondary hydroxylamines studied by Krishna, especially as they relate to biological systems. By functionalizing a second proton, particularly in a cyclical carbon ring, cyclic secondary amines present substantially different chemical reactivities, in part by reducing the availability (reactivity or nucleophilicity) of the free electron pair of the Nitrogen. This can be seen, for example, in the strikingly different redox potentials of secondary and primary hydroxylamines. Primary hydroxylamines have redox potentials in the 300 mV range (see Fig.3 of Tamilmani et al., 2003, DuPont Electronic Technology,

<http://www.ekctech.com/images/feature-stories/MRS-Interaction%20between%20ceria%20and%20Hydroxylamine.pdf>, of record), near that of the intracellular reducing potential (e.g. Sies, et al., 1977, Euro J Biochem 72, 301-7, abstract of record), whereas the cyclic secondary hydroxylamines of Krishna et al. provide redox potentials ranging from 722 to 960 mV (see, e.g. Krishna et al., 1992, PNAS USA 89, 5537-41, of record).

Krishna (1998) describes use of dozens of different compounds, but every one is a similar cyclic secondary nitroxide (and the corresponding hydroxylamines and amines). Krishna (1998) provides no suggestion or motivation to deviate from his teachings and employ a structurally and functionally distinct class of hydroxylamines, particularly since Krishna (1998) repeatedly reports that variation in redox potential across his reagents showed no significant correlation between protection and redox potentials (e.g. Krishna, 1998, at p.3488, col.2, line 41-45).


Those skilled in this art are sophisticated medicinal chemists like the present inventors and Krishna et al. who would never consider interchangeable such functionally and structurally distinct compounds as primary and secondary hydroxylamines. Note that the very subject matter of Krishna (1998) is studies of structure-activity relationship of nitroxide free radicals and their precursors (including hydroxylamines) as modifiers against oxidative damage. Krishna provides volumes of SAR data for vast numbers of hydroxylamines. Krishna, Table 1. Yet despite their stated research purpose, not a single mention is ever made of trying a primary hydroxylamine. Krishna et al. are not ignorant – to the contrary, they are experts who fully recognize that (despite the similar IUPAC nomenclature) there is no rational basis for introducing into their studies structurally and functionally dissimilar molecules like primary hydroxylamines.

Though we do not believe the cited art supports any prima facie case for obviousness, for good measure, we append an expert Declaration from Professor Ames, a present inventor and world-renowned expert in the field, averring to the foregoing facts and conclusions. Accordingly, the uncontroverted evidence of record demonstrates that the cited art would not have suggested the claimed methods to one skilled in the art at the time the invention was made.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order B00-001-2).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP


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Encl. Expert Declaration (2 p.)